
N-terminal deletion of specific phosphorylation sites on PHOX2B disrupts the formation of enteric neurons in vivo.

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Public Summary:

Mutations in the paired-like homeobox 2b (PHOX2B) gene are associated with congenital central hypoventilation syndrome (CCHS), which is a rare condition in which both autonomic dysregulation with hypoventilation and an enteric neuropathy may occur. The majority of CCHS patients have a polyalanine repeat mutation (PARM) in PHOX2B, but a minority of patients have non-polyalanine repeat mutations (NPARM), some of which have been localized to exon 1. A PHOX2B-Y14X nonsense mutation previously generated in a human pluripotent stem cell (hPSC) line results in an N-terminus truncated product missing the first 17 or 20 amino acids, possibly due to translational reinitiation at an alternate ATG start site. This N-terminal truncation in the PHOX2B protein results in the loss of two key phosphorylation residues. Though the deletion does not affect the potential for PHOX2B(Y14X/Y14X) mutant hPSC to differentiate into enteric neural crest cells (ENCC) in culture, it impedes in vivo development of neurons in an in vivo model of human aganglionic small intestine.

Scientific Abstract:

Mutations in the paired-like homeobox 2b (PHOX2B) gene are associated with congenital central hypoventilation syndrome (CCHS), which is a rare condition in which both autonomic dysregulation with hypoventilation and an enteric neuropathy may occur. The majority of CCHS patients have a polyalanine repeat mutation (PARM) in PHOX2B, but a minority of patients have non-polyalanine repeat mutations (NPARM), some of which have been localized to exon 1. A PHOX2B-Y14X nonsense mutation previously generated in a human pluripotent stem cell (hPSC) line results in an N-terminus truncated product missing the first 17 or 20 amino acids, possibly due to translational reinitiation at an alternate ATG start site. This N-terminal truncation in the PHOX2B protein results in the loss of two key phosphorylation residues. Though the deletion does not affect the potential for PHOX2B(Y14X/Y14X) mutant hPSC to differentiate into enteric neural crest cells (ENCC) in culture, it impedes in vivo development of neurons in an in vivo model of human aganglionic small intestine.

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